

Applicants: Carlos Cordon-Cardo et al.  
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**Amendment to the specification:**

Please amend the specification under the provisions of 37 C.F.R. §1.121 as follows:

Please replace the paragraph starting at page 103, line 5, with the following amended paragraph:

Antibody to the Her-2/neu gene product has been shown to inhibit the growth of breast cancer cells overexpressing Her-2/neu and to have clinical utility in treating breast cancer. We studied a recombinant, humanized anti-Her-2/neu antibody (Hereeptin the product Trastuzumab sold under the trademark HERCEPTIN) in preclinical models of human prostate cancer. The androgen-dependent CWR22 and LNCaP human prostate cancer xenograft models and androgen-independent sublines of CWR22 were used. Her-2/neu staining of the parental, androgen-dependent, and androgen-independent CWR22 tumors and LNCaP tumors demonstrated variable Her-2/neu expression. Hereeptin HERCEPTIN was administered i.p. at a dose of 20mg/kg twice weekly after the xenograft had been established. No effect of Hereeptin HERCEPTIN on tumor growth was observed in any of the androgen-independent tumors; however, significant growth inhibition was observed in both of the androgen-dependent xenograft models, CWR22 (68% growth inhibition at the completion of the experiment;  $P=0.03$  for trajectories of the average tumor volume of the groups) and LNCaP (89% growth inhibition;  $P=0.002$ ). There was a significant increase in prostate-specific antigen (PSA) index (ng PSA/ml serum/mm<sup>3</sup> tumor) in Hereeptin HERCEPTIN-treated androgen-dependent groups compared with control (CWR22, 18-fold relative to pretreatment value versus 1.0-fold,  $P=0.0001$ ; LNCaP, 2.35-

fold relative to pretreatment value versus 0.6-fold, P=0.001). When paclitaxel (6.25mg/kg s.c., five times/week) was given to animals with androgen-dependent and independent tumors, there was growth inhibition in each group. Paclitaxel and Hereeptin HERCEPTIN cotreatment led to greater growth inhibition than was seen for the agents individually. Thus, in these prostate cancer model systems, Hereeptin HERCEPTIN alone has clinical activity only in the androgen-dependent tumor and has at least an additive effect on growth, in combination with paclitaxel, in both androgen-dependent and androgen-independent tumors. Response to Hereeptin HERCEPTIN did not correlate with the PSA levels, because the PSA index markedly increased in the Hereeptin HERCEPTIN-treated group, whereas it remained constant in the control group. These results suggest the utility of Hereeptin HERCEPTIN in the treatment of human prostate cancer.